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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,780	09/25/2007	Roger Michael Eccles	P71237US0	3574

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
11/25/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,780	ECCLES ET AL.	
	Examiner	Art Unit	
	JD SCHULTZ	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-56* is/are pending in the application.

4a) Of the above claim(s) *43-50 and 52-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-42 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/11/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☒ Other: *Seq Compliance*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group 1, claims numeral 31-42 and 51, in the reply filed on April 14, 2006 is acknowledged. The traversal is on the ground(s) that the art originally recited by the examiner in the holding of lack of unity (i.e. Muratovska et al., Nucleic Acids Research, 2001, Vol. 29, No. 9, pp1852-1863) was misinterpreted, and that therefore the cited reference did not demonstrate that the claimed feature was not contribution over the prior art. Specifically, applicants assert that the instant claims require a disulfide linkage between the triphenylphosphonium (TPP) and PNA as recited in claim 31, formula I. Applicants allege that the chemical reaction pathway shown in figure 1 of Muratovska et al.cannot show a disulfide linkage between the PNA and the TPP, since although the figure of Muratovska shows a sulfur atom link to a cysteine, the sulfur atom that is shown is actually the sulfur atom that is the part of the cysteine; and therefore there is only a single sulfur atom in the figure.

It is agreed that the conjugate of Muratovska et al. does not teach a disulfide linkage. However, Muratovska et al. teaches every other aspect, including a TPP derivative linked to a PNA via a thioalklyl linkage. In fact, the only thing that Muratovska doesn't teach is the disulfide linkage. Furthermore, the disulfide linkage, for reasons as indicated below in the obviousness rejection, is considered to have been obvious to one of ordinary skill in the art at the time the invention was made. Briefly, this is because the TPP derivative containing the claimed disulfide linkage was first synthesized in 1995, well before applicants filing date, and because furthermore the use of disulfide linkages between antisense and carrier conjugates was well-known for achieving cleavage of the disulfide linkage due to the reducing environment of the

cytoplasm. Accordingly, the claims are considered to lack a special technical feature that constitutes a contribution over the prior art, and unity is thus considered to be lacking.

The requirement is still deemed proper and is therefore made FINAL.

Claim 43-50, and 52-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 31, 2009.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The disclosure contains sequences which fall under the purview of 37 CFR 1.821 through 1.825 as requiring SEQ ID NOS:, but which are not so identified. For example, the drawings and claims of the instant specification contain multiple sequences in excess of 10 nucleotides long are disclosed, and not identified by a SEQ ID NO:. Applicants should be aware that these examples may not be the only instances necessitating this notice. Applicants should carefully review the application for any further examples of failures to identify any sequences by SEQ ID NO:, and to otherwise verify that the application is in compliance.

Applicant is required to bring this application into sequence compliance as directed in 37 CFR 1.821 through 1.825 in the next substantive response to this action. This requirement will not be held in abeyance. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Status of Application/Amendment/Claims

Claims 31-56, filed April 14, 2006, are pending. Claims 43-50, and 52-56 are withdrawn pursuant to the restriction requirement mailed July 1, 2009. Claims 31-42 and 51 are the subject of the present Official action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on July 11, 2006 was filed before the mailing date of the instant first action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner, and a signed and initialed copy is enclosed herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 specifies a 8-amino-3,6-dioxanoic acid linking group for linking the PNA residue to the remainder of the carrier molecule as recited in claim 31. However, claim 31 recites only a single linker group, and this linker group does not link the PNA to the carrier molecule. There is no linker group that contacts the PNA itself; rather, the claim specifies that a thiol containing attachment group (S-Z) is linked to the PNA. Thus, it is not clear whether this linking group finds antecedent basis in "L", or some other unspecified portion of the conjugate. Clarification is required. For purposes of compact prosecution, the linker of claim 36 is considered to be attached directly to the PNA in an unspecified manner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-36, and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muratovska et al. (IDS), in view of Burns et al. (Arch. Biochem. Biophys. Vol 322(1) 60-68; 1995), and Bonfils et al. (Nucleic Acids Research Vol. 20(17) 4621-4629; 1992).

The claimed invention is drawn to a TPP-PNA conjugate, which comprises a linker group, and a sulfide linked to a thiol-containing attachment group to form a disulfide bond, and an optional anion. The linker may comprise (Ci - C30) alkylene or substituted (Cl - C30) alkylene, or may be (C3 - C10) alkylene, or may be butylene. The thiol containing attachment group may comprise cysteinyl, homocysteinyl or an aminothiol. The linking group for linking to

the PNA residue may be 8-amino-3,6-dioxanoic acid. The PNA may be attached to a molecular tag or reporter molecule, wherein the molecular tag or reporter molecule is an affinity comprising streptavidin or biotin, or wherein the reporter molecule is fluorescein.

Muratovska et al. teach a TPP-PNA conjugate comprising a butylene linker group, and an aminothiol as a thiol-containing attachment group (see figure 1). The conjugate contains 8-amino-3,6-dioxanoic acid linked to the PNA residue. The PNA is attached to a molecular tag or reporter molecule, as biotin is also attached (Materials and Methods pg. 1653). Muratovska et al. do not teach a reporter molecule, or wherein said reporter molecule may be florescein. However, Muratovska et al. does teach the use of fluorescently labeled antibodies to report the spatial location of their conjugates, which therefore meets the limitation of "reporter molecule". Florescein is a well known fluorophore To those of skill in the artand its use is considered substitutable and equivalent to any other fluorophore, absent evidence to the contrary.

Importantly, Muratovska et al. does not teach the disulfide linkage between the PNA and the linker attached to TPP. However, Burns et al. teach the synthesis and characterization of thiobutyltriphenylphosphonium bromide (TBTP), and that TBTP localizes to the mitochondria. TBTP is the instantly claimed TPP derivative, complete with disulfide bond. Bonfils et al. teach oligonucleotide targeting and intracellular internalization via conjugation to a membrane permeable peptide through a disulfide linkage which is cleaved in the reducing environment of the cytoplasm (see abstract).

It would have been obvious to one of ordinary skill in the art to substitute the disulfide containing TBTP of Burns et al. in place of the TPP of Muratovska et al. in the method of targeting TPP/PNA's conjugates to mitochondria. One of ordinary skill would have had a

reason for such a substitution, because Bonfils et al. teach that oligonucleotides bound to membrane permeable carriers that have disulfide bridges are reduced in the cytosol and are thus released from their carrier leading to an increase in efficiency of oligonucleotide driven inhibition (see abstract). Thus, it was known to one of ordinary skill in the art that carrier conjugation via disulfide linkage would allow for cleavage of carrier from oligonucleotide for increased target accessibility and reduced steric hindrance. Furthermore, one of ordinary skill would have had a reasonable expectation of success, given that both PPTP of Burns and PPP of Muratovska localized to the mitochondria, and because Muratovska et al. shows that TPP conjugation to PNA was capable of delivering said PNA's to mitochondria. Accordingly, one of ordinary skill in the art would have considered the invention to be prima facie obvious in view of the cited references at the time the invention was made.

Claims 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muratovska et al., in view of Burns et al., and Bonfils et al. as applied to claims 31-36, and 39-42 above, and further in view of Goodyer et al (WO 01/46404 A2).

The invention is as described above, further comprising the use of sequences TTCACACCCCCGTGCC, GTCCCAGACGGT or lys-GTCCCAGACGGT as PNA sequences.

Goodyer et al. teach use of a primer comprising TTCACACCCCCGTGCC to amplify PAX2. This is the same sequence as claimed in claim 37. Goodyer et al. also teach methods of using antisense oligonucleotides to inhibit human PAX2, a transcription factor associated with kidney and other diseases. While it is acknowledged that the cited sequence is not contemplated as a specific antisense target sequence in the Goodyer reference, it is known in the art that both

primers and antisense sequences are designed to be derived uniquely from the target sequence. Accordingly, one of ordinary skill in the art would have been motivated to use the primer sequence of Goodyer et al. to design antisense sequences in methods of inhibiting PAX2 as taught by Goodyer et al. One of ordinary skill in the art would have had a reasonable expectation of success since the use of PNA's in methods of inhibiting was taught successfully by Muratovska et al.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables

applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JDS

/JD SCHULTZ/
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